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Phase I Trial of Intramuscular Injection of a Recombinant Adeno-Associated Virus
Alpha 1-Antitrypsin (rAAV2-CB-hAAT) Gene Vector to AAT-Deficient Adults

Technical Abstract

Several groups have demonstrated that recombinant adeno-associated virus (rAAV) vectors are capable of sustained expression of therapeutic proteins when administered to skeletal muscle. In the case of alpha-1-antitrypsin (AAT) deficiency, a single injection of an AAV vector resulted in sustained AAT secretion at levels that would be therapeutic for humans suffering from this disorder (approximately 800 µg/ml)(96). The goal of this study, a phase I clinical trial of rAAV2-AAT gene transfer in patients with AAT deficiency is to determine the safety and biological activity of using this gene to augment serum levels of AAT in deficient patients. A single dose (dose-escalated between cohorts) of rAAV2-CMV/beta-actin promoter-AAT (CB-AAT) vector is being injected directly into the deltoid muscle of each of 12 AAT-deficient patients. The primary endpoints of the study assess safety with examinations of the injection site, hematology, chemistry, coagulation studies, and pulmonary function tests. Biological activity of the vector is primarily assessed by detection in the serum of normal M-variant AAT protein by an isoelectric focusing gel/ immunoblot technique. Serum is also assayed for antibodies to rAAV2 capsid and to AAT. Blood and semen DNA are also being assayed for vector DNA sequences.